CENTER FOR DRUG EVALUATION AND RESEARCH

74-890

APPLICATION NUMBER:

CORRESPONDENCE

noted pkg
9/23/98

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL. (847) 573-9999 • FAX (847) 573-1001

September 17, 1998

AM

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

RE: ANDA 74-890
Cimetidine Tablets USP
200 mg, 300 mg, 400 mg and 800 mg

To Whom It May Concern:

As per the deficiency letter dated July 14, 1998, from Kassandra Sherrod, Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex, Inc., is submitting this Minor Amendment in duplicate.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs

MM/ty

Enclosures

Nadine
9.23.98

Tor Pharm Inc.

COVER LETTER

MINOR AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 74-890 for Cimetidine Tablets USP 200 mg, 300 mg, 400 mg and 800 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated July 14, 1998.

David Coffin-Beach, B.S.Pharm, Ph.D.
President, TorPharm
50 Steinway Blvd.
Etobicoke, Ontario
M9W 6Y3

15 Sept 98
Date

TORPHARM

Amendment to ANDA #74-890
Cimetidine Tablets USP 200 mg,
300 mg, 400 mg and 800 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

JUL 14 1998

38. Chemistry Comments to be provided to the Applicant:

ANDA: 74-890 APPLICANT: Torpharm Inc.

DRUG PRODUCT: Cimetidine Tablets USP, 200, 300, 400 and 800 mg

The deficiencies presented below represent MINOR deficiencies:

Deficiencies:

1. The application cannot be approved until deficiencies regarding DMF have been addressed satisfactorily by the holder.

2. We still request that you establish a Purity specification for the Cimetidine USP drug substance of NLT in your drug substance testing specifications. It is recommended that you work with your DMF vendor to establish this tightened specification.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

March 20, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX AMENDMENT

RE: ANDA 74-890
Cimetidine Tablets USP
200 mg, 300 mg, 400 mg, and 800 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex, Inc., is submitting this fax amendment for deficiency fax letter dated March 10, 1998.

Please note that this response contains approximately 150 pages. Due to the size of the submission, we are faxing you the written responses. The attachments, such as referenced test specifications, will be enclosed in the original response that will be sent by mail.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald KK

Marcy Macdonald
Associate Director
Regulatory Affairs

KK/98-107

Tor Pharm Inc.

COVER LETTER

FACSIMILE AMENDMENT

TorPharm, a Division of Apotex Inc., 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 74-890 for Cimetidine Tablets USP 200 mg, 300 mg, 400 mg and 800 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated March 10, 1998.

David Coffin-Beach, B.S.Pharm, Ph.D.
President, TorPharm, a Division of Apotex Inc.
50 Steinway Blvd.
Etobicoke, Ontario
M9W 6Y3

19 March 98
Date

TORPHARM, A DIVISION OF APOTEX INC.

Amendment to ANDA #74-890
Cimetidine Tablets USP 200 mg,
300 mg, 400 mg and 800 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

MAR 10 1998

38. Chemistry Comments to be provided to the Applicant:

ANDA: 74-890 APPLICANT: TorPharm Inc.

DRUG PRODUCT: Cimetidine Tablets USP 200, 300, 400 and 800 mg

The deficiencies presented below represent FACSIMILE deficiencies:

Deficiencies:

Regarding your newly revised Related Compounds testing for Cimetidine USP:

a) Although you have included methods validation information for the new method we request that you provide further clarification regarding revision of your original method. Although you have stated that the new method provides better resolution of impurity peaks, we note that you have revised your list of detectable related compounds (impurities) from those impurities of your former method. Most notably the removal of the purities from your new list of identifiable impurities. Please clarify.

b) Please provide justification for your high RSD value of for 6 replicate injections you propose as an acceptance criteria in your methods validation. In addition, please provide typical RSD data obtained from your routine day-to-day analysis.

c) Also, since it is assumed that you intend to incorporate your revised Related Compounds testing method into your finished product testing as well as your stability protocol, you are requested to submit a revised finished product specification sheet and stability testing protocol reflecting incorporation of this new method with the revised specification limits you propose.

Sincerely yours,

John D. Harrison

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143
28101 BALLARD ROAD • LAKE FOREST • ILLINOIS 60045 • Tel: (847) 816-9350 • Fax: (847) 816-9356

MAJOR AMENDMENT

NDA CTS AMENDMENT

N/A

RECEIVED

SEP 29 1997

GENERIC DRUGS

September 26, 1997

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA # 74-890
Cimetidine Tablets USP 200 mg, 300 mg 400 mg and 800 mg

Dear Mr. Sporn:

Apotex Corp. as the U.S. agent for TorPharm Inc. of Ontario, Canada is submitting a major amendment to the above referenced ANDA.

Please feel free to contact me if you have any further questions.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs

TorPharm

COVER LETTER

MAJOR AMENDMENT

TorPharm Inc., 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 74-890 for Cimetidine Tablets USP 200 mg, 300 mg, 400 mg and 800 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated June 6, 1997.

David Coffin-Beach

24 Sept 97

David Coffin-Beach, B.S.Pharm, Ph.D.
President, TorPharm Inc.
50 Steinway Blvd.
Etobicoke, Ontario
M9W 6Y3

Date

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

JUN 6 1997

38. Chemistry Comments to be provided to the Applicant:

ANDA: 74-890 APPLICANT: TorPharm

DRUG PRODUCT: Cimetidine Tablets USP 200, 300, 400 and 800 mg

A. The deficiencies presented below represent MAJOR deficiencies:

Deficiencies:

1. Regarding the updated Certificate of Analysis you submitted for Cimetidine USP in your amendment response, it is noted that you no longer include Related Compounds specification testing for the drug substance. You should resubmit a revised COA with this test included. Also, please narrow your Particle Size testing specification. The open ended range you provide is too wide.

2. We still recommend that you perform routine blend assays on all production batches in accordance with 21 CFR. Your proposed 1 assay test in 10 is unacceptable. If you still choose to delete this testing from your standard in-process testing protocol, we would recommend you submit data in support of this deletion in the form of a prior approval supplement to the ANDA some time in the future after approval of the drug product.

3. Regarding the new equipment you propose, it is noted that the and the have the same operating principle; however, they have different designs. After working with both pieces of equipment, you have decided to manufacture future production batches using the or although the biobatch was manufactured using the . You have also included information on the You are requested to provide data supporting the use of the over the which was used in the manufacture of the biobatch. Also, data should be provided to support the proposed settings uded in the Master batch records for the use of the which differs considerably from the process parameters listed for the used for the biobatch manufacture. OGD Policy and Procedure Guide #22-90 states that the submission batch and the production batch should be manufactured on equipment of the "same design and operating principle."

4. In accordance with 21 CFR, once the in-process specification limits for bulk density and particle size analysis have been established, you are to include the in-process specification testing limits in the batch records for future manufacturing purposes. Please revise and resubmit.

5. With respect to your manufacturing process as presented in the flow diagram, please clarify the difference between magnesium stearate addition and

magnesium stearate addition.

6. With regard to your proposal of a _ period for granulation prior to compression, we note that the data are not complete. You only provide data for the 200 and 800 mg strength tablets. Also, you have only provided assay testing results. In order to justify a 6 month holding time for the granulation and to ensure that the quality of the drug product is not compromised, full stability testing data should be provided for all strengths of tablets compressed from granulation lots that were stored for 6 months. This would include all stability tests in your proposed stability protocol. Also, please clarify that the expiration dating period would begin at the time of granulation not compression.

7. Your in-process testing protocol remains unsatisfactory. As mentioned above, we recommend that you include routine blend homogeneity in your testing protocol. Also, you did not provide a clear list of all in-process testing for future production batches *with* testing limits as requested. In process testing specifications should be reviewed by the Agency prior to approval of the drug product and should be included in the batch records at the time of approval.

8. Since the majority of the instability in tablet formulations occurs due to moisture in the tablets, it is still recommended that you include a test for moisture in your finished product and stability testing protocol. This is in accordance with FDA Guidelines. Please submit a revised Certificate of Analysis and revised stability protocol.

B. In addition to responding to the deficiencies present above, please note and acknowledge the following comment in your response:

Regarding your request for an alternate stability protocol you submitted as a new correspondence on April 10, 1997, we recommend that you withdraw your request at this time and resubmit all required data as a supplement to the ANDA post-approval.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

file 1cs
4/17/97

APOTEX CORP.

1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143
28101 BALLARD ROAD • LAKE FOREST • ILLINOIS 60045 • Tel: (847) 816-9350 • Fax: (847) 816-9356

April 10, 1997

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

14890

RE: General Inquiry
Request for Alternate Stability Protocol

Dear Mr. Sporn:

As the U.S. agent for TorPharm Inc. of Ontario, Canada, Apotex Corp. is submitting a general inquiry to request approval of an alternate stability protocol.

We appreciate an expeditious review of this information.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Manager, Regulatory Affairs

RECEIVED
APR 14 1997
GENERIC DRUGS

Marcy 4/11/97

S1 copy only

APOTEX USA INC.

1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143

MAJOR AMENDMENT ORIG AMENDMENT

N/A

March 7, 1997

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA # 74-890
Cimetidine Tablets USP, 200 mg, 300 mg, 400 mg & 800 mg
Response to Communication of September 27, 1996

Dear Sir:

We are writing in response to your communication of September 27, 1996 concerning the above referenced ANDA. We will respond to the items as presented.

We appreciate an expeditious review of this information. If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Manager, Regulatory Affairs

RECEIVED

MAR 1 1 1997

GENERIC DRUGS

ANDA 74-890

Apotex USA, Inc.
U.S. Agent for: Torpharm, Inc.
Attention: Marcy Macdonald
1641 Barclay Boulevard
Buffalo Grove IL 60089-4544

SEP 30 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cimetidine Tablets USP, 200 mg, 300 mg, 400 mg, and 800 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing should be conducted as specified in the USP 23 and should be incorporated into your stability and quality control programs.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-890

Apotex USA, Inc.
U.S. Agent for: Torpharm Inc.
Attention: Marcy Macdonald
1641 Barclay Blvd.
Buffalo Grove, IL 60089-4544

SEP 27 1996

Dear Ms. Macdonald:

This is in reference to your abbreviated new drug application dated April 19, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Tablets USP, 200 mg, 300 mg, 400 mg, and 800 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Comments

9/27/96

protocol to include testing for moisture.
Reasonable specification limits should be set.

B. Labeling Deficiencies:

1. CONTAINER - 30s (800 mg), 60s (400 mg), 100s (200 mg and 300 mg), 500s (400 mg and 800 mg), 1000s (200 mg and 300 mg).

   a. Revise the storage statement to read "Store at controlled room temperature 15°-30°C (59°-86°F)."

   b. Include the statement "Usual Dosage: See package insert." You mention this statement is not to appear until final printed labels are done (p 20). Why was this statement not included initially?

2. INSERT

   a. DESCRIPTION

      Please confirm your tablets are imprinted and include any dyes contained in the imprinting ink(s) in the list of inactive ingredients.

   b. CLINICAL PHARMACOLOGY

      Clinical Trials, Active Benign Gastric Ulcer, Tables - "Total at week 6" (Delete extra space between "at" and "week").

   c. OVERDOSAGE

      i. Paragraph 1 - ... tachycardia that may ...

      ii. Paragraph 4 - ... adults who were reported...

d. DOSAGE AND ADMINISTRATION

i. Active Duodenal Ulcer

A). Paragraph 1 - ... healing (see CLINICAL PHARMACOLOGY, Antisecretory Activity - Acid Secretion). This is ... trials (see CLINICAL PHARMACOLOGY, Clinical Trials - Active Duodenal Ulcer). Therefore ...

B). Paragraph 5 - ... bedtime (see CLINICAL PHARMACOLOGY, Clinical Trials - Active Duodenal Ulcer).

ii. Active Benign Gastric Ulcer, sentence 2 - ... treatment (see CLINICAL PHARMACOLOGY, Clinical Trials). 800 mg ...

e. HOW SUPPLIED

i. Insert the following text as the first paragraph:

Cimetidine Tablets USP are available as:

ii. See comment a under CONTAINER.

iii. We encourage you to include the color of the imprinted markings.

Please revise your container labels and package insert labeling, as instructed above, and submit 12 copies of final printed container labels and package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial

disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

9/27/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-890

MAY 14 1996

Apotex USA, Inc.
U.S. Agents for: TorPharm, Inc.
Attention: Anton Amann, Ph.D.
1641 Barclay Blvd.
Buffalo Grove, IL 60089-4544

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Cimetidine Tablets USP, 200 mg, 300 mg, 400 mg, and 800 mg

DATE OF APPLICATION: April 19, 1996

DATE OF RECEIPT: April 22, 1996

We also acknowledge your correspondence dated May 8, 1996.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 594-1300

Sincerely yours,

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX USA INC.

1641 Barclay Boulevard • Buffalo Grove • Illinois 60089-4544 • FAX 708.541.1143

RECEIVED

APR 22 1996

GENERIC DRUGS

April 19, 1996

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Via Federal Express

RE: Original ANDA Submission
Cimetidine Tablets, USP 200, 300 400 and 800 mg

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal, Food, Drug and Cosmetic Act as amended September 24, 1984, Apotex USA, Inc. as US agent for TorPharm Inc. of Ontario, Canada, hereby submits an original abbreviated new drug application for Cimetidine Tablets, USP 200, 300, 400 and 800 mg.

We are submitting an archival copy under a blue cover (14 volumes), a chemistry review copy plus an additional copy of the analytical methods section under a red cover (9 volumes) and the bioavailability/bioequivalence review section under an orange cover (7 volumes). Enclosed with the bioequivalence copy is a diskette that contains the raw data from which these reports were derived. Another copy of the diskette can be found with the blue archival copy.

Apotex, USA hereby certifies that in accordance with 21 CFR 314.94 (d)(5) a true field copy of the technical sections of this submission has been sent to the International and Technical Operations Branch under a burgundy cover (copy of cover letter enclosed).

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the address listed above.

Sincerely,

Anton Amann, Ph.D.
Senior Vice President
Scientific Operations